An Example of Automated Liquid Chromatography. Synthesis of a Broad-Spectrum Resolving Agent and Resolution of 1-(1-Naphthyl)-2,2,2-trifluoroethanol

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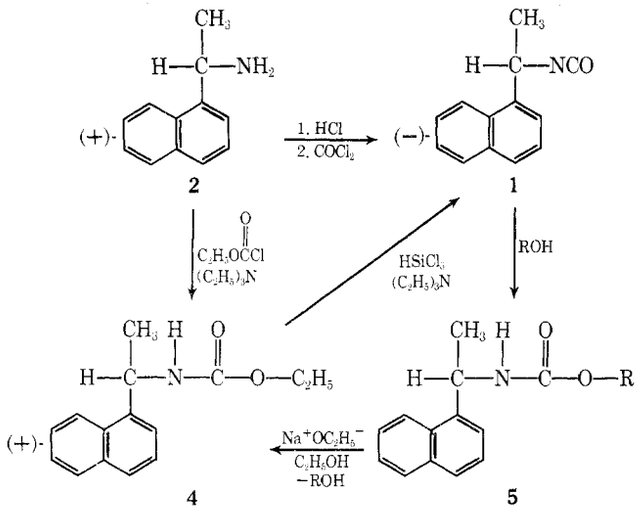
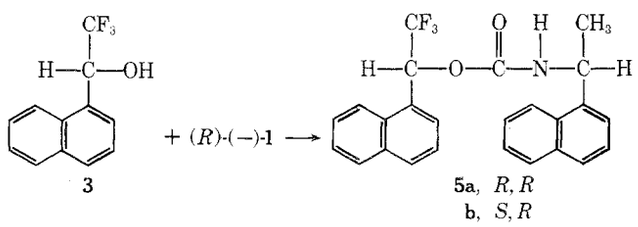
Resolved 1-(1-naphthyl)ethyl isocyanate (**1**), a useful reagent for the chromatographic resolution, *via* diastereomeric derivatives of a variety of alcohols, α-hydroxy esters, and thiols, can be prepared by the action of phosgene on the hydrochloride of amine **2**, or by treatment of ethyl carbamate **4** of amine **2** with trichlorosilane; however, no **1** is obtained when **4** is treated with trimethylchlorosilane. The diastereomeric carbamates derived from racemic 1-(1-naphthyl)-2,2,2-trifluoroethanol (**3**) and chiral 1-(1-naphthyl)ethyl isocyanate (**1**) are readily separable *via* automated preparative liquid chromatography. Ethanolysis of the separated diastereomers affords both enantiomers of the resolved alcohol and a recoverable form of the resolving agent.

While optical resolutions have frequently been effected *via* chromatographic separation of diastereomeric derivatives, this has seldom been the preferred approach for preparative scale work. Moreover, no chiral derivatizing reagent has previously been recommended for the chromatographic resolution of a broad spectrum of derivatizable enantiomers.[2] Since we have found it possible, on a preparative scale, to separate chromatographically the diastereomeric derivatives (**4**) formed when enantiomeric 1-(1-naphthyl)ethyl isocyanate (**1**) is allowed to react with any of a number of racemic alcohols, α-hydroxy esters, and thiols,[3] and since subsequent hydrolysis of the separated diastereomers can then afford the resolved alcohols or thiols, we report here our evaluation of three synthetic routes to this useful resolving agent, beginning with commercial (*R*)-(+)-1-(1-naphthyl)ethylamine (**2**). Furthermore, we illustrate the use of this reagent in the resolution of 1-(1-naphthyl)-2,2,2-trifluoroethanol (**3**). Resolved fluoro alcohol **3**, considerably more effective as a chiral nmr solvent than the previously used phenyl analog,[4] has until now been obtained with difficulty since conventional methods for its resolution have been tedious and generally unsatisfactory.[5] In addition to being widely applicable, the resolution method illustrated here is convenient, is efficient in terms of material and labor, affords both enantiomers, and regenerates the resolving agent. In combination with a newly developed automated preparative liquid chromatography system,[6] the present method makes feasible the resolution of multigram quantities of numerous alcohols, amines,[7] and thiols. We further point out that most of the diastereomeric carbamates thus far encountered are crystalline after (and sometimes before) separation. In these cases there exists the possibility of separating the diastereomers by fractional crystallization.[8]

Three possible synthetic routes to isocyanate **1** from amine **2** were considered. The analogous preparation of (*R*)-(−)-1-phenylethyl isocyanate by the action of phosgene on the corresponding amine hydrochloride has been reported.[9] In the case of amine **2**, this method affords isocyanate **1** almost quantitatively, the only hindrance being the toxicity of phosgene. The recently reported method of isocyanate synthesis involving treatment of carbamates with trimethylchlorosilane[10] failed to give detectable (nmr) amounts of isocyanate **1** when applied to the ethyl carbamate **4**, prepared by reaction of amine **2** with ethyl chloroformate. However, under similar conditions, trichlorosilane readily converts ethyl carbamate **4** into isocyanate **1**, thereby offering a second route to **1** which avoids phosgene. This second synthesis is of a particular value since, after separation, the diastereomeric carbamates **5** can be cleaved by the action of ethanolic sodium ethoxide into the resolved alcohol and ethyl carbamate **4**. Hence this synthetic scheme offers a convenient means of recovering the resolving agent.



An example of the use of isocyanate **1** as a resolving agent is provided by the resolution of fluoro alcohol **3**. Isocyanate (*R*)-(−)-**1** reacts cleanly with an equimolar quantity of racemic alcohol **3** at 80° to afford a syrupy mixture of the diastereomeric carbamates (**5a** and **5b**) which is readily separable by chromatography on alumina with benzene, provided the ratio of alumina to carbamate is 2500:1 or greater. Chromatography of 1-g portions of this mixture with benzene on a 2.5 in. × 48 in. column of acidic alumina cleanly separates the diastereomers (α 1.37) as determined by absorbance monitoring at 280 nm. Using the system described,[6] 6–10 g of the diastereomeric mixture may be separated per 24-hr period.[11] Figure 1 illustrates the repetitive chromatographic separation of diastereomeric carbamates **5a** and **5b**.



The *R,R* diastereomer is eluted first and both diastereomers are, once separated, readily recrystallized from hexane. Treatment of either diastereomer with ethanolic sodium ethoxide cleanly liberates chiral fluoro alcohol **3** and affords ethyl *N*-(1-[1-naphthyl]ethyl)carbamate (**4**) which is easily separable from **3** and is reconvertible to isocyanate **1**.

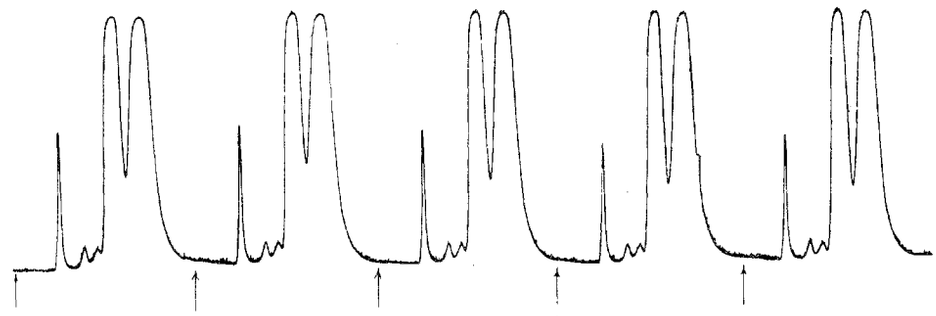


Figure 1. The automated repetitive chromatographic separation of diastereomeric carbamates **5a** and **5b** on acidic alumina with benzene. The separability factor, α, is 1.37. The *R,R* diastereomer **5a** is the first of the two major bands; minor absorptions are caused by impurities. Sample injections of 1 g (arrows) occur every 3 hr. Because of saturation of the 280-nm detector, the extent of peak overlap appears to be greater than is actually the case.

Experimental Section

Melting points were taken on a Büchi apparatus and are uncorrected. Optical rotations were determined at 589 nm in a Zeiss visual polarimeter, using a 1.0-dm tube. Infrared spectra were measured with a Perkin-Elmer 521 or a Perkin-Elmer 237B spectrophotometer. Nmr spectra were obtained with a Varian A-60-D spectrometer. Mass spectra were determined by J. C. Cooke and his associates, using a Varian MAT CH-5 spectrometer. Microanalyses were performed by J. Nemeth and his colleagues.

(*R*)-(+)-1-(1-Naphthyl)ethylamine (2). Resolved material having a rotation $\alpha^{28.3}$ +80.47 ± 0.05° (neat, l = 1) was obtained from Norse Chemical Co., and was used without further purification.

(*R*)-(−)-1-(1-Naphthyl)ethyl Isocyanate (1). A. Phosgene Method. In a 1000-ml three-necked flask fitted with a reflux condenser, mechanical stirrer, and gas inlet tube, amine (*R*)-(+)-**2** (17.13 g, 0.10 mol) was dissolved in dry toluene (200 ml). The solution was stirred, and dry hydrogen chloride was added through the inlet tube, which was placed with the opening above the liquid level, to prevent plugging. After most of the white, solid 1-(1-naphthyl)ethylamine hydrochloride had formed, the inlet tube was lowered into the mixture and more hydrogen chloride was added to assure that the solution was saturated. Additional dry toluene (100 ml) was added, and phosgene was slowly and continuously bubbled into the mixture, which, after a few minutes, was heated to reflux for 4 hr. At this point, all solid had disappeared, leaving a straw-colored solution. The toluene was distilled at reduced pressure, the residual liquid was transferred to a 100-ml flask and distilled to afford colorless isocyanate (*R*)-(−)-**1** (19.02 g, 96.3%): bp 106–108° (0.16 mm); $[\alpha]^{24.1}$ −50.5 ± 0.2° (*c* 27.9, benzene); ir (neat) 2260 (N=C=O), 795, and 775 cm^{-1}; nmr ($CDCl_3$) δ 1.60 (d, 3, J = 6.7 Hz, CH_3), 5.38 (quartet, 1, J = 6.7 Hz, CH), and 7.21–8.04 ppm (m, 7, $C_{10}H_7$); mass spectrum (70 eV) *m/e* (rel intensity) 197 (71, M^+), 182 (100), 155 (40), 154 (13), 128 (21), 127 (35).

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10. Found: C, 79.03; H, 5.66; N, 6.95.

B. Trichlorosilane Method. To a stirred solution of ethyl carbamate (*R*)-(+)-**4** (24.33 g, 0.10 mol) and triethylamine (11.13 g, 0.11 mol) in dry benzene (200 ml), a solution of trichlorosilane (14.90 g, 0.11 mol) in dry benzene (50 ml) was added dropwise, over a 15-min period. After 30 min, the solution was heated to reflux for 30 min, allowed to cool to room temperature, and filtered under nitrogen to remove triethylamine hydrochloride. Removal of the solvent at reduced pressure left a cloudy yellow liquid, which was distilled under vacuum to give isocyanate (*R*)-(−)-**1** (16.4–16.7 g, 83.1–84.6%), identical by nmr and ir with that prepared by the phosgene method, $[\alpha]^{23.4}$D −50.8 ± 0.5° (*c* 32.9, benzene).

The preparation of isocyanate **1** from amine **2** using the trichlorosilane sequence may be carried out without isolation of the intermediate ethyl carbamate **4**; the overall yield is not substantially altered. Thus into a stirred solution of amine (*R*)-(+)-**2** (17.12 g, 0.10 mol) and triethylamine (11.13 g, 0.11 mol) was rapidly poured a solution of ethyl chloroformate (12.28 g of 97%, 0.11 mol) in dry benzene (50 ml). The mixture was stirred for 30 min, heated to reflux for 30 min, and allowed to cool. Filtration under nitrogen to remove triethylamine hydrochloride gave a clear yellow solution to which additional triethylamine (11.13 g, 0.11 mol) was added. The solution was stirred, and a solution of trichlorosilane (14.90 g, 0.11 mol) in dry benzene (50 ml) was added dropwise over a 15-min period. After a 30-min period, the solution was heated to reflux for 30 min, then allowed to cool to room temperature, and filtered under nitrogen to remove triethylamine hydrochloride. Removal of the solvent at reduced pressure left a brown liquid sometimes containing a solid which was removed by filtration after dissolving the isocyanate in dry pentane. After pentane removal, vacumm distillation gave isocyanate (*R*)-(−)-**1** (14.07 g, 71.4%).

(*R*)-(+)-Ethyl *N*-(-[1-Naphthyl]ethyl)carbamate (4). Into a stirred solution of amine (*R*)-(+)-**2** (17.12 g, 0.10 mol) and triethylamine (11.13 g, 0.11 mol) in dry benzene (150 ml) was rapidly poured a solution of ethyl chloroformate (12.28 g of 97%, 0.11 mol) in dry benzene (50 ml). After stirring for 30 min, the mixture was heated to reflux for 30 min, then allowed to cool. The mixture was then filtered to remove triethylamine hydrochloride, and concentrated at reduced pressure to afford crude crystalline **4** (24.4 g). Recrystallization from benzene–petroleum ether affords ethyl carbamate (*R*)-(+)-**4** (20.63 g, 84.8%): mp 99.9–100.3°; $[\alpha]^{23}$D +22.7 ± 0.1° (*c* 19.9, chloroform); ir (KBr) 3325 (NH), 1683 (C=O), 1546, 1258, 1059, 788, and 769 cm^{-1}; nmr ($CDCl_3$) δ 1.18 (t, 3, CH_2CH_3), 1.61 (d, 3, $CHCH_3$), 4.10 (quartet, 2, CH_2CH_3), 5.06 (d, broad, 1, NH) 5.63 (d of quartet, 1, NH-C*H*-CH_3) and 7.20–8.20 ppm (m, 7, $C_{10}H_7$).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found C, 74.33; H, 7.11; N, 6.05.

***dl*-1-(1-Naphthyl)-2,2,2-trifluoroethanol (3).** A solution of lithium trifluoroacetate, prepared by addition of lithium hydride (8.0 g, 1.0 mol) to trifluoroacetic acid (101 g, 0.89 mol) in dry tetrahydrofuran (200 ml), was added over a 10-min period to the Grignard reagent prepared from 1-bromonaphthalene (207 g, 1.0 mol) and magnesium turnings (25 g, 1.0 mol) in dry ether (950 ml). After a 1-hr reflux period, 6 *M* hydrochloric acid was added with cooling until the mixture was acidic, and the organic layer was collected after addition of pentane (500 ml). The crude 1-naphthyl trifluoromethyl ketone (243 g), isolated by solvent evaporation, was not purified, but was mixed with methanol (200 ml) and reduced by portionwise addition of sodium borohydride (12 g, 0.32 mol). This solution was diluted with water (1000 ml), acidified with hydrochloric acid, and twice extracted with 200-ml portions of methylene chloride. The solvent was removed at reduced pressure and the residual oil was dissolved in a solution of potassium hydroxide in aqueous methanol (prepared from 260 g of potassium hydroxide, 160 ml of water, and 1440 ml of methanol). The resulting solution (in which the desired fluoro alcohol **3** is present in anionic form) was extracted several times with 200-ml portions of pentane in order to remove naphthalene and binaphthyl. The bulk of the methanol was removed at reduced pressure, water (1000 ml) was added, and the resulting solution was acidified with 12 *M* hydrochloric acid. Extraction with three 200-ml portions of methylene chloride, drying of the extracts, and removal of the solvent at reduced pressure, followed by distillation of the resulting oil, gave *dl*-**3**, which solidified in the receiving flask (116 g, 0.51 mol, 58%): bp 83–85° (0.025 mm); mp 47.4–48.5° (recrystallized from hexane); ir (neat liquid) 3410 (OH), 1270, 1165, 1120, 795, and 780 cm^{-1}; nmr ($CDCl_3$) δ 3.24 (s, 1, OH), 5.62 (quartet, 1, CH), and 7.16–7.96 ppm (m, 7, $C_{10}H_7$); mass spectrum (70 eV) *m/e* (rel intensity) 226 (40, M^+), 157 (80, $[M - CF_3]^+$), 129 (100), 128 (54), 127 (38).

Anal. Calcd for $C_{12}H_9F_3O$: C, 63.72; H, 4.01. Found: C, 63.77; H, 3.98.

1-(1-Naphthyl)-2,2,2-trifluoroethyl *N*-(1-[1-Naphthyl]ethyl)carbamate (5a, 5b). Racemic fluoro alcohol **3** (6.20 g, 0.27 mol) and isocyanate (*R*)-(−)-**1** (5.34 g, 0.27 mol) were mixed and heated to 80° while protected by a drying tube, for 65 hr,[12] by which time the isocyanate band at 2260 cm^{-1} had disappeared. The mixture

was then automatically chromatographed with benzene on a 2.5 × 48 in. column of Brinkmann acidic alumina. The effluent was monitored at 280 nm.

The first major fraction to be eluted was (*R,R*)-(+)-**5a** (4.34 g, 0.010 mol, 75.0%). Recrystallization from hexane gave white needles: mp 139.7–140.6°; ir (KBr) 3325 (NH), 1728, 1696, 1532, 1514, 1270, 1242, 1183, 1174, 1064, 801, and 779 cm^{-1}; nmr ($CDCl_3$) δ 1.54 (d, 3 $CHCH_3$), 5.48 (s, 1, NH), 5.54 (quartet, 1, $CHCH_3$), 7.03 (quartet, 1, $CHCF_3$), and 7.16–8.28 ppm (m, 14, both $C_{10}H_7$); $[\alpha]^{26.7}D$ +56.1 ± 1.1° (*c* 3.65, chloroform).

Anal. Calcd for $C_{25}H_{20}F_3NO_2$: C, 70.91; H, 4.76; N, 3.31. Found: C, 70.78; H, 4.77; N, 3.47.

The second major fraction to be eluted was (*S,R*)-(−)-**5b** (5.62, 0.013 mol, 97.0%), which can be recrystallized from hexane: mp 123.1–124.0°; ir 3450 (NH) 1724, 1505, 1264, 1232, 1180, 1167, 1127, 1061, 790, and 769 cm^{-1}; nmr ($CDCl_3$) δ 1.46 (d, 3, $CHCH_3$), 5.55 (s, 1, NH) 5.58 (quartet, 1, $CHCH_3$), 7.02 (quartet, 1, $CHCF_3$), and 7.20–8.28 ppm (m, 14, both $C_{10}H_7$); $[\alpha]^{24.5}D$ −12.2 ± 0.3° (*c* 15.5, chloroform).

Anal. Calcd for $C_{25}H_{20}F_3NO_2$: C, 70.91; H, 4.76; N, 3.31. Found: C, 71.05; H, 4.78; N, 3.41.

Conversion of (*R,R*)-(+)-1-(1-Naphthyl)-2,2,2-trifluoroethyl *N*-(1-[1-Naphthyl]ethyl)carbamate (5a) to (*R*)-(−)-(1-Naphthyl)-2,2,2-trifluoroethanol (3). Carbamate (*R,R*)-(+)-**5a** (4.23 g, 0.01 mol) was added to a solution of ethanolic sodium ethoxide (2.5 g sodium in 30 ml of ethanol) and refluxed for 30 min, at which time tlc (silica gel–methylene chloride) showed no remaining **5a**. The ethanol was removed at reduced pressure and excess base was neutralized with dilute hydrochloric acid. The aqueous mixture was extracted with three 50-ml portions of methylene chloride and the combined extracts were dried, concentrated, and chromatographed automatically with methylene chloride on a 2.5 × 48 in. column of Brinkmann silica gel.

The first major band to be eluted was fluoro alcohol[13] (*R*)-(−)-**3** (2.17 g, 0.0096 mol, 95.7%) identical by nmr, ir, and tlc to racemic **3**. Molecular distillation gave a waxy solid: mp 51.6–53.2°; $[\alpha]^{25.3}D$ −25.7 ± 0.7° (*c* 5.1, ethanol).

The second fraction contained, upon removal of the solvent, (*R*)-(+)-ethyl *N*-(1-[1-naphthyl]ethyl)carbamate (2.02 g, 0.0083 mol, 83.1%), identified by nmr.

A similar hydrolysis of carbamate (*S,R*)-(−)-**5b** gave, after chromatography, fluoro alcohol (*S*)-(+)-**3**: mp 51.6–53.6°; $[\alpha]^{25.7}D$ +25.8 ± 0.5° (*c* 5.1, ethanol).

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Registry No.—(*R*)-**1**, 42340-98-7; (*R*)-**2**, 3886-70-2; *dl*-**3**, 17556-44-4; (*R*)-**3**, 22038-90-0; (*S*)-**3**, 33758-06-4; (*R*)-**4**, 53043-11-1; (*R,R*)-**5a**, 53043-12-2; (*S,R*)-**5b**, 53043-13-3; trifluoroacetic acid, 76-05-1; 1-bromonaphthalene, 90-11-9.

References and Notes

(1) (a) Alfred P. Sloan Foundation Research Fellow, 1970–1974. (b) Phillips Petroleum Predoctoral Fellow, 1972–1974.
(2) In view of the widespread separability of the diastereomeric derivatives of **1**, it is clear that this reagent, in conjunction with a high-pressure analytical liquid chromatography system, offers a useful tool for the determination of optical purity of those enantiomeric compounds which form derivatives with **1**.
(3) While a more comprehensive report of this resolution method will appear later, a partial list of compounds whose diastereomeric derivatives with **1** have been separated chromatographically on a preparative scale is as follows: 1-phenyl-2,2,2-trifluoroethanol; 1-phenyl-2,2,2-trichloroethanol; 1-phenyl-2,2,2-tribromoethanol; 1-(1-naphthyl)-2,2,2-trifluoroethanol; 1-(2-naphthyl-2,2,2-trifluoroethanol; 1-(3-pyrenyl)-2,2,2-trifluoroethanol; 1-(9-anthryl)-2,2,2-trifluoroethanol; 1-(10-methyl-9-anthryl)-2,2,2-trifluoroethanol; 1-phenyl-2,2,3,3,4,4,4-heptafluoro-1-butanol; 1-phenylethanol; 1-(4-nitrophenyl)ethanol; 1-(4-methoxyphenyl)ethanol; 1-(1-naphthyl)ethanol; 1-(2-naphthyl)ethanol; 1-phenylethanethiol; ethyl 2-mercaptopropanoate; methyl 2-hydroxy-3,3-dimethylbutanoate; methyl mandelate; 1-cyclohexyl-2,2,2-trifluoroethanol; 3-hydroxy-3-phenyl-4,4,4-trifluoro-1-butyne.
(4) W. H. Pirkle, R. L. Muntz, and I. C. Paul, *J. Amer. Chem. Soc.*, **93**, 2817 (1971), and references therein.
(5) R. L. Muntz, Ph.D. Thesis, University of Illinois, Urbana, 1972.
(6) W. H. Pirkle and R. W. Anderson, *J. Org. Chem.*, **39**, 3901 (1974).
(7) The use of racemic isocyanates and chiral alcohols or, alternatively, racemic amines and chiral chloroformates, will afford diastereomeric carbamates which may be separated and hydrolyzed.
(8) The phenyl analog of this isocyanate, commercially available for several years, has previously been used [H. W. Gschwend, *J. Amer. Chem. Soc.*, **94**, 8430 (1972)] to afford diastereomers separable by crystallization. We are unaware of prior examples of chromatographic separation of diastereomeric carbamates derived from 1-phenylethyl isocyanate. In point of fact, we have found that the diastereomeric carbamates of this isocyanate do not, in general, separate as well chromatographically as those derived from **1**.
(9) T. L. Cairns, *J. Amer. Chem. Soc.*, **63**, 871 (1941).
(10) G. Greber and H. R. Kricheldorf, *Angew. Chem.*, **80**, 1028 (1968).
(11) In the event unreacted alcohol or other strongly retained materials are present in the crude product, a rough large-scale prechromatography may be desirable.
(12) Use of 1% of either *N,N*-dimethylethanolamine or di-*n*-butyltin dilaurate as a catalyst reduces reaction times to as little as *ca.* 10 hr.
(13) The absolute configuration of fluoro alcohol **3** has been established previously by the chiral nmr solvent method, using a partially resolved sample. See W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, **89**, 5485 (1967). Subsequent work in these laboratories further supports the assignment.

Base-Catalyzed Decomposition of 1,2,3-Selenadiazoles and Acid-Catalyzed Formation of Diselenafulvenes

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The kinetics and mechanism of the base-catalyzed decomposition of 4-aryl-1,2,3-selenadiazole with arylethynylselenolate ion as the intermediate and the subsequent hydrogen ion catalyzed formation of substituted 1,3-diselenafulvenes from this intermediate in basic alcoholic media have been investigated. Details of the mechanism, rate constants, and dependence upon the acidity function H_- are reported and discussed. An interesting coupling of the various steps in the above processes under certain conditions has been found and analyzed in some detail.

The mechanism of the formation of the 1,3-diselenafulvenes has previously been reported.[2] The steps of this reaction can be summarized as in Scheme I.

While Scheme I, deduced from our experimental observations, adequately describes the results, several points remained to be clarified. These were (a) the importance of the equilibrium in step 1 as opposed to an irreversible and concerted hydrogen abstraction–decomposition to the ethynylselenolate ion, and (b) the extent of the equilibrium in step 3 and thus a measure of the stability of the heretofore unknown selenaketene. By undertaking a kinetic study of the reaction we hoped to gain a better understanding of the